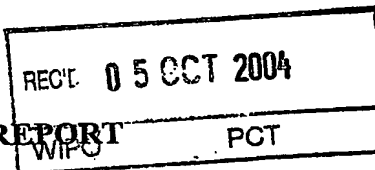


PATENT COOPERATION TREATY
PCT
INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)



Applicant's or agent's file reference 12360940/JMS:ETC	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International Application No. PCT/IB2003/004177	International Filing Date (day/month/year) 18 August 2003	Priority Date (day/month/year) 16 August 2002
International Patent Classification (IPC) or national classification and IPC Int. Cl. ⁷ C07D 405/04, 403/04, 471/04, A61K 31/519, 31/355, 31/4709, A61P 7/02		
Applicant KINACIA PTY LTD et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


2. This REPORT consists of a total of 5 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 17 sheet(s).

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 3 March 2004	Date of completion of the report 23 September 2004
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer  S.R. IDRUS Telephone No. (02) 6283 2659

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/IB2003/004177

I. Basis of the report

1. With regard to the elements of the international application:*

☐ the international application as originally filed.☒ the description, pages 1-66, as originally filed,

pages , filed with the demand,

pages , received on with the letter of

☒ the claims, pages , as originally filed,

pages , as amended (together with any statement) under Article 19,

pages , filed with the demand,

pages 67-83, received on 30 August 2004 with the letter of 30 August 2004

☒ the drawings, pages 1/7-7/7, as originally filed,

pages , filed with the demand,

pages , received on with the letter of

☐ the sequence listing part of the description:

pages , as originally filed

pages , filed with the demand

pages , received on with the letter of

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).☐ the language of publication of the international application (under Rule 48.3(b)).☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.☐ filed together with the international application in computer readable form.☐ furnished subsequently to this Authority in written form.☐ furnished subsequently to this Authority in computer readable form.☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished4. ☐ The amendments have resulted in the cancellation of:☐ the description, pages☐ the claims, Nos.☐ the drawings, sheets/fig.5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/IB2003/004177

II. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be nonobvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos: 1, and 2

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claim Nos. 1, and 2

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/IB2003/004177

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 1-25	YES
	Claims	NO
Inventive step (IS)	Claims 1-25	YES
	Claims	NO
Industrial applicability (IA)	Claims 1-25	YES
	Claims	NO

2. Citations and explanations (Rule 70.7)

No international search report has been established for Claims 1 and 2. Thus the opinion given in relation to Claims 1 and 2 only relate to citations revealed by the search that was conducted.

The International Search Report, however, identified the following citations:

D1) WO 2001/053266

D2) WO 1991/019707

D3) WO 1990/006921

D4) EP 0 341 104

D5) US 5703075

D6) C. J. VLAHOS et. al., The Journal of Biological Chemistry

D7) J. MORRIS et. al., Journal of Med. Chem.,

D8) C. W. BENJAMIN et. al., The Journal of Pharmacology and Experimental Therapeutics

D9) C. W. BENJAMIN et. al., Developments in Oncology

D10) STN File CA Abstract Accession No. 139:133525

D11) STN File CA Abstract Accession No. 138:287191

D12) STN File CA Abstract Accession No. 116:214192

D13) STN File CA Abstract Accession No. 63:31556

D14) STN File CA Abstract Accession No. 62:49088

D15) STN File CA Abstract Accession No. 56:73359

D16) STN File CA Abstract Accession No. 48:64297

D4 disclosed substituted flavonoid compounds useful as medicaments including as inhibitors of platelet agglutination. However, it does not teach or fairly suggest any anti-platelet therapy employing the characteristics of the PI 3-kinase beta isoform of the present invention. Accordingly, Claims 4, and 14-18 are novel and involve inventive step in the light of this citation.

Claim 5 of the present application is novel and involves inventive step in the light of D4, D12, D13, D14, D15, and D16.

Supplemental Box

To be used when the space in any of the preceding boxes is not sufficient)

Continuation of Box V

D10 and **D11** disclosed compounds falling within the scope of Claim 5 of the present application but they are published after the priority date. These citations therefore do not render Claim 5 not novel.

While Claims 1 and 2 were not searched, the search conducted did reveal documents which were relevant to said Claims 1 and 2.

The compounds disclosed in **D2**, **D3** and **D5** are excluded from Claim 2 of the present application. While these citations disclosed methods for the prevention or treatment of thrombotic diseases they do not teach or fairly suggest any anti-platelet therapy employing the characteristics of the PI 3-kinase beta isoform of the present invention. Accordingly, Claim 2 is novel and involves inventive step in the light of these citations.

D6 disclosed a series of Phosphatidylinositol 3-Kinase (PI3-Kinase) inhibitors which are excluded from Claim 2 of the present application. Accordingly, Claim 2 is novel in the light of this citation. Moreover, while the citation disclosed the inhibition of PI3-Kinase by the series of inhibitors disclosed it does not teach or fairly suggest any anti-platelet therapy employing the characteristics of the PI 3-kinase beta isoform of the present invention. Accordingly, Claim 2 and consequently Claim 1 involve inventive step in the light of this citation.

D7 disclosed a series of inhibitors of ADP induced platelet aggregation which are excluded from Claim 2 of the present application. Accordingly, Claim 2 is novel in the light of this citation. Moreover, while the citation disclosed preventing platelet-dependent thrombus formation by the series of inhibitors disclosed it does not teach or fairly suggest any anti-platelet therapy employing the characteristics of the PI 3-kinase beta isoform of the present invention. Accordingly, Claim 2 involves inventive step in the light of this citation.

D8 and **D9** disclosed method of evaluating the antithrombotic activity of a series of inhibitory agents such as U-84569 which are excluded from Claim 2 of the present application. Accordingly, Claim 2 is novel in the light of this citation. Moreover, while the citation disclosed inhibition of human platelet aggregation by said agents it does not teach or fairly suggest any anti-platelet therapy employing the characteristics of the PI 3-kinase beta isoform of the present invention. Accordingly, Claim 2 involves inventive step in the light of this citation.

D1 disclosed anti-thrombotic morpholino substituted pyrido[1,2-a]pyrimid-4-one compounds which are excluded from Claim 2 and Claim 3 of the present application. Accordingly, Claims 2 and 3 are novel in the light of this citation. Moreover, while the compounds of the citation are described as inhibitors of PI 3-kinase, the present invention employs the characteristics of the PI 3-kinase beta isoform as a prerequisite to shear-induced platelet aggregation. Accordingly, Claim 2 and consequently Claim 1 and Claim 3 also involve inventive step in the light of this citation.

Claim 7 differs from Claim 2 by virtue of the different morpholino substituted pyrido[1,2-a]pyrimid-4-one compounds used and in turn the morpholino substituted pyrido[1,2-a]pyrimid-4-one compounds of Claim 7 differs from those of this citation by the linker used, namely, an "amino ethyl" moiety. Accordingly, Claim 7 is novel in the light of this citation. Moreover, it has been conceded above that Claim 2 of the present invention employs the characteristics of the PI 3-kinase beta isoform as a prerequisite to shear-induced platelet aggregation. Accordingly, Claim 7 also involves inventive step in the light of this citation.

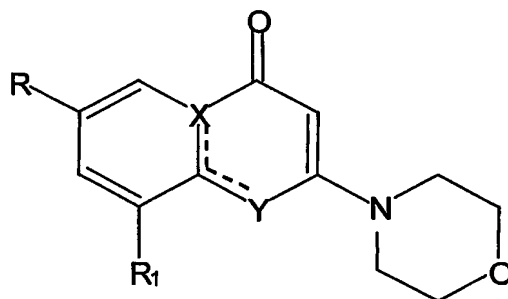
Similarly, Claims 4, 6 and 21-25 are novel and involve inventive step in the light of this citation.

The subject matter of Claims 1-25 are useful in antithrombotic therapy and screening methods therefor. Accordingly Claims 1-25 are industrially applicable.

Claims

1. A method of disrupting platelet aggregation and adhesion occurring under high shear conditions comprising administering an effective amount of a selective PI 3-kinase β inhibitor to a patient in need thereof.

2. (Amended) A method for antithrombosis comprising administering an effective amount of a selective PI 3-kinase β inhibitor to a patient in need thereof,



provided that the inhibitor is not according to formula (II):

(II)

wherein,

where X and Y are C and O respectively, or C and NH respectively, or both N

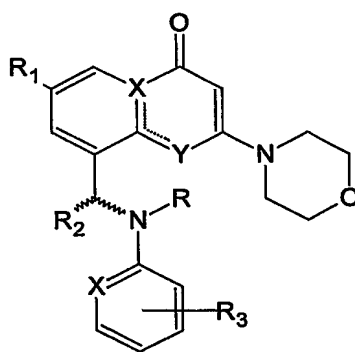
R is H, OH, F, Cl, Br, I, C₁-C₆ alkyl, aryl or (CH₂)_n-aryl;

R¹ is H, OH, F, Cl, Br, I, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, CH=CH-aryl, C≡C-aryl, (CHR³)_n-aryl, NR³-C₁-C₆ alkyl, NR³-cycloalkyl, NR³-(CHR³)_n-aryl, (CHR³)_n-NR³-alkyl, (CHR³)_n-NR³-cycloalkyl, (CHR³)_n-O-aryl, (CHR³)_n-O-alkyl, (CHR³)_n-O-cycloalkyl, O-(CHR³)_n-aryl, S-(CHR³)_n-aryl, or CO-aryl, wherein n is 0, 1, or 2 and alkyl, cycloalkyl or aryl is optionally substituted with F, Cl, Br, I, CN, CO₂H, CO₂R³, NO₂, CF₃, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, OCF₃, OR³, OSO₂-aryl, substituted or unsubstituted amine, NHCOR³, NH₂SO₂R³, CONHR³, or SO₂NHR³; and

R^3 is H, or substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted aryl;
except where the compound of formula (II) is selected from the group consisting of:

9-(3-pyridinylmethyl)oxy-2-morpholinyl-4H-pyrido[1,2-a]pyrimidin-4-one (TGX-140);
7-methyl-9-phenylaminomethyl-2-morpholinyl-4H-pyrido[1,2-a]pyrimidin-4-one (TGX-183);
8-(4-methylphenyl)-2-(4-morpholinyl)-4(1H)-quinolinone (TGX-113);
8-(4-fluorophenoxy)-2-(4-morpholinyl)-4(1H)-quinolinone (TGX-121);
2-morpholinyl-8-(phenylmethyl)-4H-1-benzopyran-4-one (TGX-90);
2-(4-morpholinyl)-8-(4-fluoro-2-methylphenyl)oxy-4H-1-benzopyran-4-one (TGX-184);
7-methyl-9-(*N*-Methyl-*N*-phenyl)aminomethyl-2-(4-morpholinyl)-4H-pyrido[1,2-a]pyrimidin-4-one (TGX-195);
2-(4-morpholinyl)-8-(phenylmethyl)amino-4H-1-benzopyran-4-one (TGX-204);
2-(4-morpholinyl)-8-phenylamino-4H-1-benzopyran-4-one (TGX-324);
8-(3-chlorophenyl)oxy-2-(4-morpholinyl)-4H-1-benzopyran-4-one (TGX-259);
8-(3-methylphenyl)-2-(4-morpholinyl)-4(1H)-quinolinone (TGX-127);
8-(2-fluorophenyl)-2-(4-morpholinyl)-4(1H)-quinolinone (TGX-143);
(±)-7-methyl-2-morpholin-4-yl-9-[1-(3-pyridinylamino)ethyl]-pyrido[1,2-a]pyrimidin-4-one (KN-304).

3. The method of claim 2, wherein the selective PI 3-kinase β inhibitor is according to formula (I):



wherein,

R is H, C_1 - C_6 branched or straight chain alkyl, or aryl or $(CH_2)_n$ -aryl;

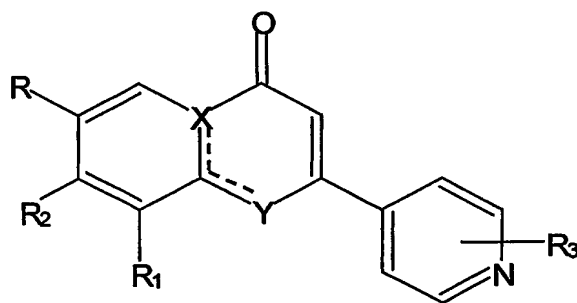
R₁ is H, OH, OCH₃, OCF₃, F, Cl, CF₃, C₁-C₆ branched or straight chain alkyl, or aryl or (CH₂)_n-aryl;

R₂ is C₁-C₆ branched or straight chain alkyl, or aryl or (CH₂)_n-aryl in either the R or the S configuration

R₃ is one or more of H, F, Cl, Br, I, CN, CO₂H, CO₂R, NO₂, CF₃, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, OCH₃, OCH₂F, OCHF₂, OCF₃, OR, OSO₂-aryl, substituted or unsubstituted amine, NHCOR, NHSO₂R, CONHR, or SO₂NHR

X is C or N and Y is N or O.

4. (Amended) The method of claim 2, wherein the selective PI 3-kinase β inhibitor is according to formula (III):



(III)

(A) where X and Y are C and O respectively

R is H, OH, OCH₃, OCF₃, F, Cl, Br, I, C₁-C₆ alkyl, aryl or (CH₂)_n-aryl;

R₁ is H, OH, F, Cl, Br, I, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, CH=CH-aryl, C≡C-aryl, (CHR'³)_n-aryl, NR'³-C₁-C₆ alkyl, NR'³-cycloalkyl, NR'³-(CHR'³)_n-aryl, (CHR'³)_n-NR'³-aryl, (CHR'³)_n-NR'³-alkyl, (CHR'³)_n-NR'³-cycloalkyl, (CHR'³)_n-O-aryl, (CHR'³)_n-O-cycloalkyl, O-

$(\text{CHR}^{'3})_n$ -aryl, S- $(\text{CHR}^{'3})_n$ -aryl, or CO-aryl, wherein n is 0, 1, or 2, $(\text{CHR}^{'3})_m$ -O-alkyl wherein m is 1 or 2, and cycloalkyl or aryl is optionally substituted with F, Cl, Br, I, CN, CO_2H , $\text{CO}_2\text{R}^{'3}$, NO_2 , CF_3 , substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, OCF_3 , $\text{OR}^{'3}$, OSO_2 -aryl, substituted or unsubstituted amine, $\text{NHCOR}^{'3}$, $\text{NH}\text{SO}_2\text{R}^{'3}$, $\text{CONHR}^{'3}$, or $\text{SO}_2\text{NHR}^{'3}$ and alkyl is optionally substituted with F, Cl, Br, I, CN, NO_2 , CF_3 , substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, OCF_3 , OSO_2 -aryl, substituted or unsubstituted amine, $\text{NHCOR}^{'3}$, $\text{NH}\text{SO}_2\text{R}^{'3}$, $\text{CONHR}^{'3}$, or $\text{SO}_2\text{NHR}^{'3}$;

R_2 and R_3 are independently H, OH, F, Cl, Br, I, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, $\text{CH}=\text{CH}$ -aryl, $\text{C}\equiv\text{C}$ -aryl, $(\text{CHR}^{'3})_n$ -aryl, $\text{NR}^{'3}$ - C_1 - C_6 alkyl, $\text{NR}^{'3}$ -cycloalkyl, $\text{NR}^{'3}$ -($\text{CHR}^{'3})_n$ -aryl, $(\text{CHR}^{'3})_n$ - $\text{NR}^{'3}$ -aryl, $(\text{CHR}^{'3})_n$ - $\text{NR}^{'3}$ -alkyl, $(\text{CHR}^{'3})_n$ - $\text{NR}^{'3}$ -cycloalkyl, $(\text{CHR}^{'3})_n$ -O-aryl, $(\text{CHR}^{'3})_n$ -O-alkyl, $(\text{CHR}^{'3})_n$ -O-cycloalkyl, O-($\text{CHR}^{'3})_n$ -aryl, S-($\text{CHR}^{'3})_n$ -aryl, or CO-aryl, wherein n is 0, 1, or 2 and alkyl, cycloalkyl or aryl is optionally substituted with F, Cl, Br, I, CN, CO_2H , $\text{CO}_2\text{R}^{'3}$, NO_2 , CF_3 , substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, OCF_3 , $\text{OR}^{'3}$, OSO_2 -aryl, substituted or unsubstituted amine, $\text{NHCOR}^{'3}$, $\text{NH}\text{SO}_2\text{R}^{'3}$, $\text{CONHR}^{'3}$, or $\text{SO}_2\text{NHR}^{'3}$; and

$\text{R}^{'3}$ is H, or substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted aryl or

(B) where X and Y are C and NH respectively

R is H, OH, OCH_3 , OCF_3 , F, Cl, Br, I, C_1 - C_6 alkyl, aryl or $(\text{CH}_2)_n$ -aryl;

R_1 , R_2 and R_3 are independently H, OH, F, Cl, Br, I, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, $\text{CH}=\text{CH}$ -aryl, $\text{C}\equiv\text{C}$ -aryl, $(\text{CHR}^{'3})_n$ -aryl, $\text{NR}^{'3}$ - C_1 - C_6 alkyl, $\text{NR}^{'3}$ -cycloalkyl, $\text{NR}^{'3}$ -($\text{CHR}^{'3})_n$ -aryl, $(\text{CHR}^{'3})_n$ - $\text{NR}^{'3}$ -aryl, $(\text{CHR}^{'3})_n$ - $\text{NR}^{'3}$ -alkyl, $(\text{CHR}^{'3})_n$ - $\text{NR}^{'3}$ -cycloalkyl, $(\text{CHR}^{'3})_n$ -O-aryl, $(\text{CHR}^{'3})_n$ -O-alkyl, $(\text{CHR}^{'3})_n$ -O-cycloalkyl, O-($\text{CHR}^{'3})_n$ -aryl, S-($\text{CHR}^{'3})_n$ -aryl, or CO-aryl, wherein n is 0, 1, or 2 and alkyl, cycloalkyl or aryl is optionally substituted with F, Cl, Br, I, CN, CO_2H , $\text{CO}_2\text{R}^{'3}$, NO_2 , CF_3 , substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, OCF_3 , $\text{OR}^{'3}$, OSO_2 -aryl, substituted or unsubstituted amine, $\text{NHCOR}^{'3}$, $\text{NH}\text{SO}_2\text{R}^{'3}$, $\text{CONHR}^{'3}$, or $\text{SO}_2\text{NHR}^{'3}$; and

R'^3 is H, or substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted aryl or

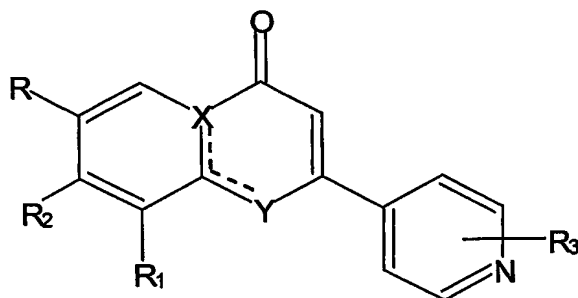
(C) where X and Y are both N

R is H, OH, OCH_3 , OCF_3 , F, Cl, Br, I, C_1 - C_6 alkyl, aryl or $(CH_2)_n$ -aryl;

R_1 , R_2 and R_3 are independently H, OH, F, Cl, Br, I, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, $CH=CH$ -aryl, $C\equiv C$ -aryl, $(CHR'^3)_n$ -aryl, NR'^3 - C_1 - C_6 alkyl, NR'^3 -cycloalkyl, NR'^3 -(CHR'^3) $_n$ -aryl, $(CHR'^3)_n$ - NR'^3 -aryl, $(CHR'^3)_n$ - NR'^3 -alkyl, $(CHR'^3)_n$ - NR'^3 -cycloalkyl, $(CHR'^3)_n$ -O-aryl, $(CHR'^3)_n$ -O-alkyl, $(CHR'^3)_n$ -O-cycloalkyl, O-(CHR'^3) $_n$ -aryl, S-(CHR'^3) $_n$ -aryl, or CO-aryl, wherein n is 0, 1, or 2 and alkyl, cycloalkyl or aryl is optionally substituted with F, Cl, Br, I, CN, CO_2H , $CO_2R'^3$, NO_2 , CF_3 , substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, OCF_3 , OR'^3 , OSO_2 -aryl, substituted or unsubstituted amine, $NHCO R'^3$, $NHSO_2 R'^3$, $CONHR'^3$, or $SO_2NHR'^3$; and

R'^3 is H, or substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted aryl.

5. (Amended) A compound having the following formula (III):



(III)

(A) where X and Y are C and O respectively

R is H, OH, OCH_3 , OCF_3 , F, Cl, Br, I, C_1 - C_6 alkyl, aryl or $(CH_2)_n$ -aryl;

R_1 is OH, F, Br, I, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, $CH=CH$ -aryl, $C\equiv C$ -aryl, $(CHR'^3)_n$ -aryl, NR'^3 - C_1 - C_6 alkyl, NR'^3 -cycloalkyl, NR'^3 -(CHR'^3) $_n$ -aryl, $(CHR'^3)_n$ - NR'^3 -aryl, $(CHR'^3)_n$ - NR'^3 -alkyl, $(CHR'^3)_n$ - NR'^3 -cycloalkyl, $(CHR'^3)_n$ -O-aryl, $(CHR'^3)_n$ -O-cycloalkyl, O-(CHR'^3) $_n$ -aryl, S-(CHR'^3) $_n$ -aryl, or CO-aryl, wherein n is 0, 1, or 2, $(CHR'^3)_m$ -O-alkyl wherein m is 1 or 2, and cycloalkyl or aryl is optionally substituted with F, Cl, Br, I, CN, CO_2H , $CO_2R'^3$, NO_2 , CF_3 , substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, OCF_3 , OR'^3 , OSO_2 -aryl, substituted or unsubstituted amine, $NHCOR'^3$, $NHSO_2R'^3$, $CONHR'^3$, or $SO_2NHR'^3$ and alkyl is optionally substituted with F, Cl, Br, I, CN, NO_2 , CF_3 , substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, OCF_3 , OSO_2 -aryl, substituted or unsubstituted amine, $NHCOR'^3$, $NHSO_2R'^3$, $CONHR'^3$, or $SO_2NHR'^3$;

R_2 and R_3 are independently H, OH, F, Cl, Br, I, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, $CH=CH$ -aryl, $C\equiv C$ -aryl, $(CHR'^3)_n$ -aryl, NR'^3 - C_1 - C_6 alkyl, NR'^3 -cycloalkyl, NR'^3 -(CHR'^3) $_n$ -aryl, $(CHR'^3)_n$ - NR'^3 -aryl, $(CHR'^3)_n$ - NR'^3 -alkyl, $(CHR'^3)_n$ - NR'^3 -cycloalkyl, $(CHR'^3)_n$ -O-aryl, $(CHR'^3)_n$ -O-alkyl, $(CHR'^3)_n$ -O-cycloalkyl, O-(CHR'^3) $_n$ -aryl, S-(CHR'^3) $_n$ -aryl, or CO-aryl, wherein n is 0, 1, or 2 and alkyl, cycloalkyl or aryl is optionally substituted with F, Cl, Br, I, CN, CO_2H , $CO_2R'^3$, NO_2 , CF_3 , substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, OCF_3 , OR'^3 , OSO_2 -aryl, substituted or unsubstituted amine, $NHCOR'^3$, $NHSO_2R'^3$, $CONHR'^3$, or $SO_2NHR'^3$; and

R'^3 is H, or substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted aryl, or

(B) where X and Y are C and NH respectively,

R is H, OH, OCH_3 , OCF_3 , F, Cl, Br, I, C_1 - C_6 alkyl, aryl or $(CH_2)_n$ -aryl;

R_1 is OH, F, Cl, Br, I, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, $CH=CH$ -aryl, $C\equiv C$ -aryl, $(CHR'^3)_n$ -aryl, NR'^3 - C_1 - C_6 alkyl, NR'^3 -cycloalkyl, NR'^3 -(CHR'^3) $_n$ -aryl, $(CHR'^3)_n$ - NR'^3 -aryl, $(CHR'^3)_n$ - NR'^3 -alkyl, $(CHR'^3)_n$ - NR'^3 -cycloalkyl, $(CHR'^3)_n$ -O-aryl, $(CHR'^3)_n$ -O-alkyl, $(CHR'^3)_n$ -O-cycloalkyl, O-(CHR'^3) $_n$ -aryl, S-(CHR'^3) $_n$ -aryl, or CO-aryl, wherein n is 0, 1, or 2 and alkyl, cycloalkyl or aryl is optionally substituted with F, Cl, Br, I, CN, CO_2H , $CO_2R'^3$, NO_2 , CF_3 , substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted cycloalkyl, substituted or

unsubstituted aryl, OCF_3 , OR^{33} , OSO_2 -aryl, substituted or unsubstituted amine, NHCOR^{33} , $\text{NHSO}_2\text{R}^{33}$, CONHR^{33} , or $\text{SO}_2\text{NHR}^{33}$;

R_2 and R_3 are independently H, OH, F, Cl, Br, I, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, $\text{CH}=\text{CH}$ -aryl, $\text{C}\equiv\text{C}$ -aryl, $(\text{CHR}^{33})_n$ -aryl, NR^{33} - C_1 - C_6 alkyl, NR^{33} -cycloalkyl, NR^{33} -(CHR^{33}) $_n$ -aryl, $(\text{CHR}^{33})_n$ - NR^{33} -aryl, $(\text{CHR}^{33})_n$ - NR^{33} -alkyl, $(\text{CHR}^{33})_n$ - NR^{33} -cycloalkyl, $(\text{CHR}^{33})_n$ -O-aryl, $(\text{CHR}^{33})_n$ -O-alkyl, $(\text{CHR}^{33})_n$ -O-cycloalkyl, O-(CHR^{33}) $_n$ -aryl, S-(CHR^{33}) $_n$ -aryl, or CO-aryl, wherein n is 0, 1, or 2 and alkyl, cycloalkyl or aryl is optionally substituted with F, Cl, Br, I, CN, CO_2H , CO_2R^{33} , NO_2 , CF_3 , substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, OCF_3 , OR^{33} , OSO_2 -aryl, substituted or unsubstituted amine, NHCOR^{33} , $\text{NHSO}_2\text{R}^{33}$, CONHR^{33} , or $\text{SO}_2\text{NHR}^{33}$; and

R^{33} is H, or substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted aryl or

(C) where X and Y are both N

R is H, OH, OCH_3 , OCF_3 , F, Cl, Br, I, C_1 - C_6 alkyl, aryl or $(\text{CH}_2)_n$ -aryl;

R_1 is OH, F, Cl, Br, I, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, $\text{CH}=\text{CH}$ -aryl, $\text{C}\equiv\text{C}$ -aryl, $(\text{CHR}^{33})_n$ -aryl, NR^{33} - C_1 - C_6 alkyl, NR^{33} -cycloalkyl, NR^{33} -(CHR^{33}) $_n$ -aryl, $(\text{CHR}^{33})_n$ - NR^{33} -aryl, $(\text{CHR}^{33})_n$ - NR^{33} -alkyl, $(\text{CHR}^{33})_n$ - NR^{33} -cycloalkyl, $(\text{CHR}^{33})_n$ -O-aryl, $(\text{CHR}^{33})_n$ -O-alkyl, $(\text{CHR}^{33})_n$ -O-cycloalkyl, O-(CHR^{33}) $_n$ -aryl, S-(CHR^{33}) $_n$ -aryl, or CO-aryl, wherein n is 0, 1, or 2 and alkyl, cycloalkyl or aryl is optionally substituted with F, Cl, Br, I, CN, CO_2H , CO_2R^{33} , NO_2 , CF_3 , substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, OCF_3 , OR^{33} , OSO_2 -aryl, substituted or unsubstituted amine, NHCOR^{33} , $\text{NHSO}_2\text{R}^{33}$, CONHR^{33} , or $\text{SO}_2\text{NHR}^{33}$;

R_2 and R_3 are independently H, OH, F, Cl, Br, I, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, $\text{CH}=\text{CH}$ -aryl, $\text{C}\equiv\text{C}$ -aryl, $(\text{CHR}^{33})_n$ -aryl, NR^{33} - C_1 - C_6 alkyl, NR^{33} -cycloalkyl, NR^{33} -(CHR^{33}) $_n$ -aryl, $(\text{CHR}^{33})_n$ - NR^{33} -aryl, $(\text{CHR}^{33})_n$ - NR^{33} -alkyl, $(\text{CHR}^{33})_n$ - NR^{33} -cycloalkyl, $(\text{CHR}^{33})_n$ -O-aryl, $(\text{CHR}^{33})_n$ -O-alkyl, $(\text{CHR}^{33})_n$ -O-cycloalkyl, O-(CHR^{33}) $_n$ -aryl, S-(CHR^{33}) $_n$ -aryl, or CO-aryl, wherein n is 0, 1, or 2 and alkyl, cycloalkyl or aryl is optionally substituted with F, Cl, Br, I, CN, CO_2H , CO_2R^{33} , NO_2 , CF_3 , substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted

cycloalkyl, substituted or unsubstituted aryl, OCF₃, OR'³, OSO₂-aryl, substituted or unsubstituted amine, NHCOR'³, NHSO₂R'³, CONHR'³, or SO₂NHR'³; and

R'³ is H, or substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted aryl.

6. The method of claim 2, comprising administering the 2-morpholino-substituted derivative of formula (I) wherein:

R is H, C₁-C₆ branched or straight chain alkyl or aryl;

R₁ is H, OH, OCH₃, OCF₃, F, Cl, CF₃, C₁-C₆ branched or straight chain alkyl;

R₂ is C₁-C₆ branched or straight chain alkyl, or aryl in either the R or the S configuration

R₃ is one or more of H, F, Cl, Br, CN, CO₂H, CO₂R, NO₂, CF₃, branched or straight chain C₁-C₆ alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, OCH₃, OCH₂F, OCHF₂, OCF₃, OR, substituted or unsubstituted amine, NHCOR, NHSO₂R, CONHR, or SO₂NHR

X is C or N and Y is N or O.

7. The method of claim 2, wherein the inhibitor administered is selected from the group consisting of:

(±)-7-methyl-9-{{methyl(phenyl)amino}methyl}-2-morpholin-4-yl-pyrido[1,2-a]pyrimidin-4-one (TGX-195);

(±)-7-methyl-2-morpholin-4-yl-9-(1-phenylaminoethyl)-pyrido[1,2-a]pyrimidin-4-one (TGX-221);

(±)-7-methyl-2-morpholin-4-yl-9-[1-(4-fluorophenylamino)ethyl]-pyrido[1,2-a]pyrimidin-4-one (TGX-224);

(±)-9-[1-(3,4-difluorophenylamino)ethyl]-7-methyl-2-morpholin-4-yl-pyrido[1,2-a]pyrimidin-4-one (TGX-237);

(±)-9-[1-(2,5-difluorophenylamino)ethyl]-7-methyl-2-morpholin-4-yl-pyrido[1,2-a]pyrimidin-4-one (TGX-238);

(±)-9-[1-(3,5-difluorophenylamino)ethyl]-7-methyl-2-morpholin-4-yl-pyrido[1,2-a]pyrimidin-4-one (TGX-239);

(±)-9-[1-(4-fluoro-2-methylphenylamino)ethyl]-7-methyl-2-morpholin-4-yl-pyrido[1,2-a]pyrimidin-4-one (TGX-240);

(±)-9-[1-(4-chlorophenylamino)ethyl]-7-methyl-2-morpholin-4-yl-pyrido[1,2-a]pyrimidin-4-one (TGX-243);

(±)-9-[1-(3,4-dichlorophenylamino)ethyl]-7-methyl-2-morpholin-4-yl-pyrido[1,2-a]pyrimidin-4-one (TGX-244);

(±)-9-[1-(3-fluorophenylamino)ethyl]-7-methyl-2-morpholin-4-yl-pyrido[1,2-a]pyrimidin-4-one (TGX-247);

(±)-9-[1-(3-chlorophenylamino)ethyl]-7-methyl-2-morpholin-4-yl-pyrido[1,2-a]pyrimidin-4-one (TGX-248);

(±)-7-methyl-2-morpholin-4-yl-9-[1-(2-thiazolylamino)ethyl]-pyrido[1,2-a]pyrimidin-4-one (TGX-261);

(±)-7-methyl-9-[1-(3-methylphenylamino)ethyl]-2-morpholin-4-yl-pyrido[1,2-a]pyrimidin-4-one (TGX-262);

(±)-7-methyl-2-morpholin-4-yl-9-[1-(3-trifluoromethylphenylamino)ethyl]-pyrido[1,2-a]pyrimidin-4-one (TGX-264); and

(±)-7-methyl-2-morpholin-4-yl-9-[1-(2-pyridinylamino)ethyl]-pyrido[1,2-a]pyrimidin-4-one (TGX-295).

(±)-2-({1-[7-methyl-2-(morpholin-4-yl)-4-oxo-pyrido[1,2-a]pyrimidin-9-yl]ethyl}amino)benzoic acid (KN-309);

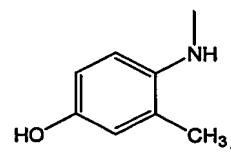
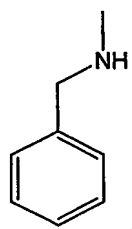
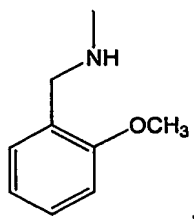
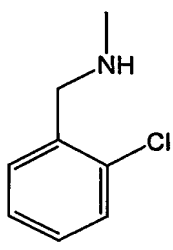
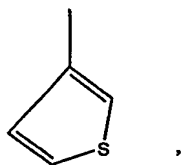
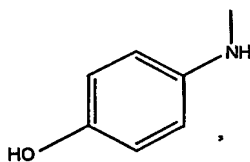
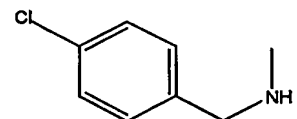
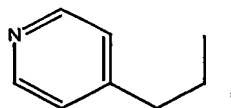
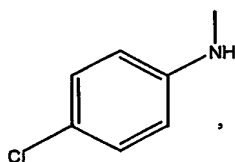
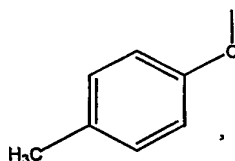
(±) methyl 2-({1-[7-methyl-2-(morpholin-4-yl)-4-oxo-pyrido[1,2-a]pyrimidin-9-yl]ethyl}amino)benzoate (KN-321);

(±)-2-({1-[7-methyl-2-(morpholin-4-yl)-4-oxo-pyrido[1,2-a]pyrimidin-9-yl]ethyl}amino)benzonitrile (KN-320);

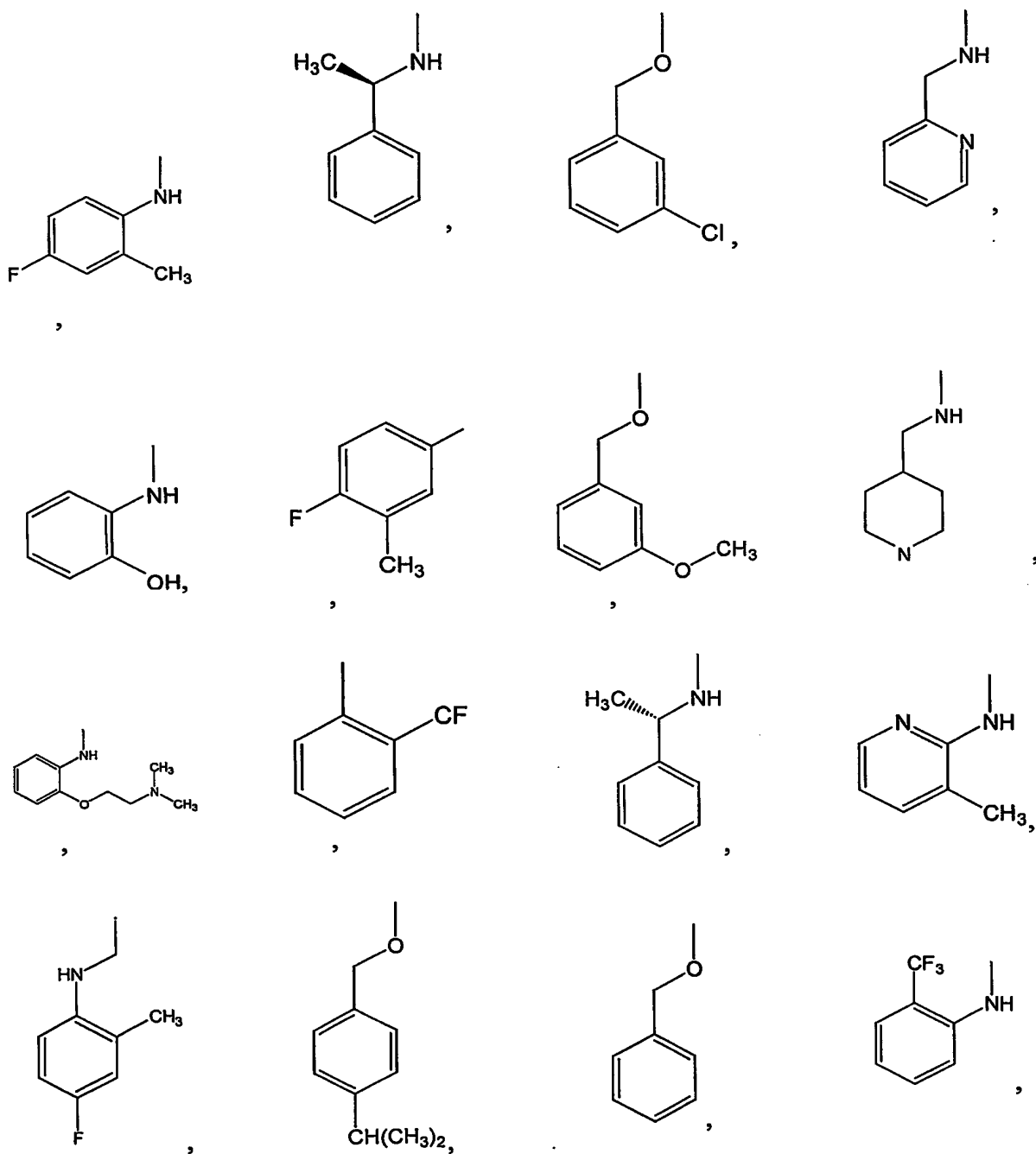
(±)-7-methyl-2-(morpholin-4-yl)-9-(1-{[2-(2*H*-tetrazol-5-yl)phenyl]amino}ethyl)-pyrido[1,2-a]pyrimidin-4-one (KN-325);

(±)-2-(4-morpholinyl)-8[1-(phenylamino)ethyl]-4*H*-1-benzopyran-4-one (TGX-280).

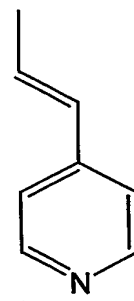
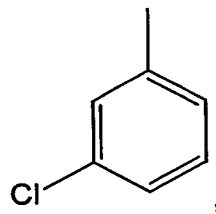
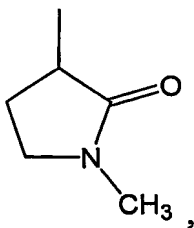
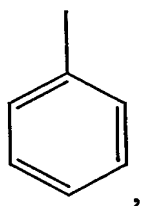
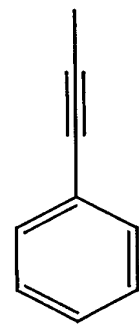
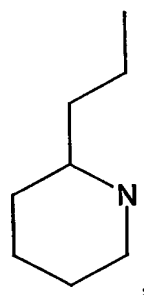
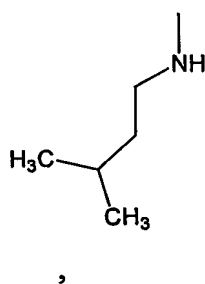
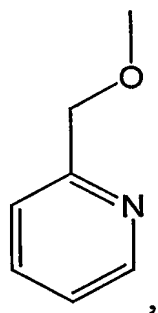
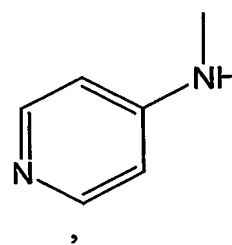
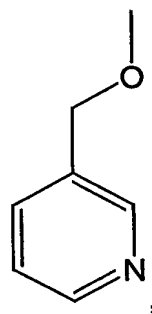
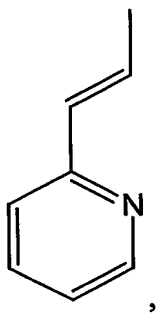
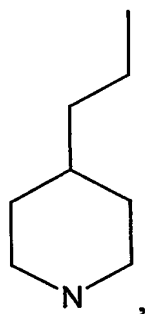
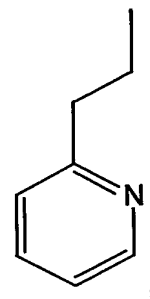
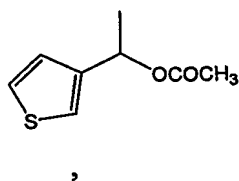
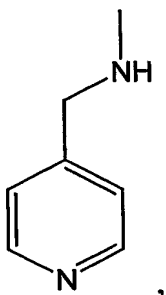
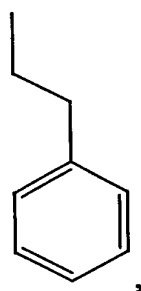
8. The compound of claim 5, wherein R¹ is selected from a group consisting of, CH₃, C₂H₅,

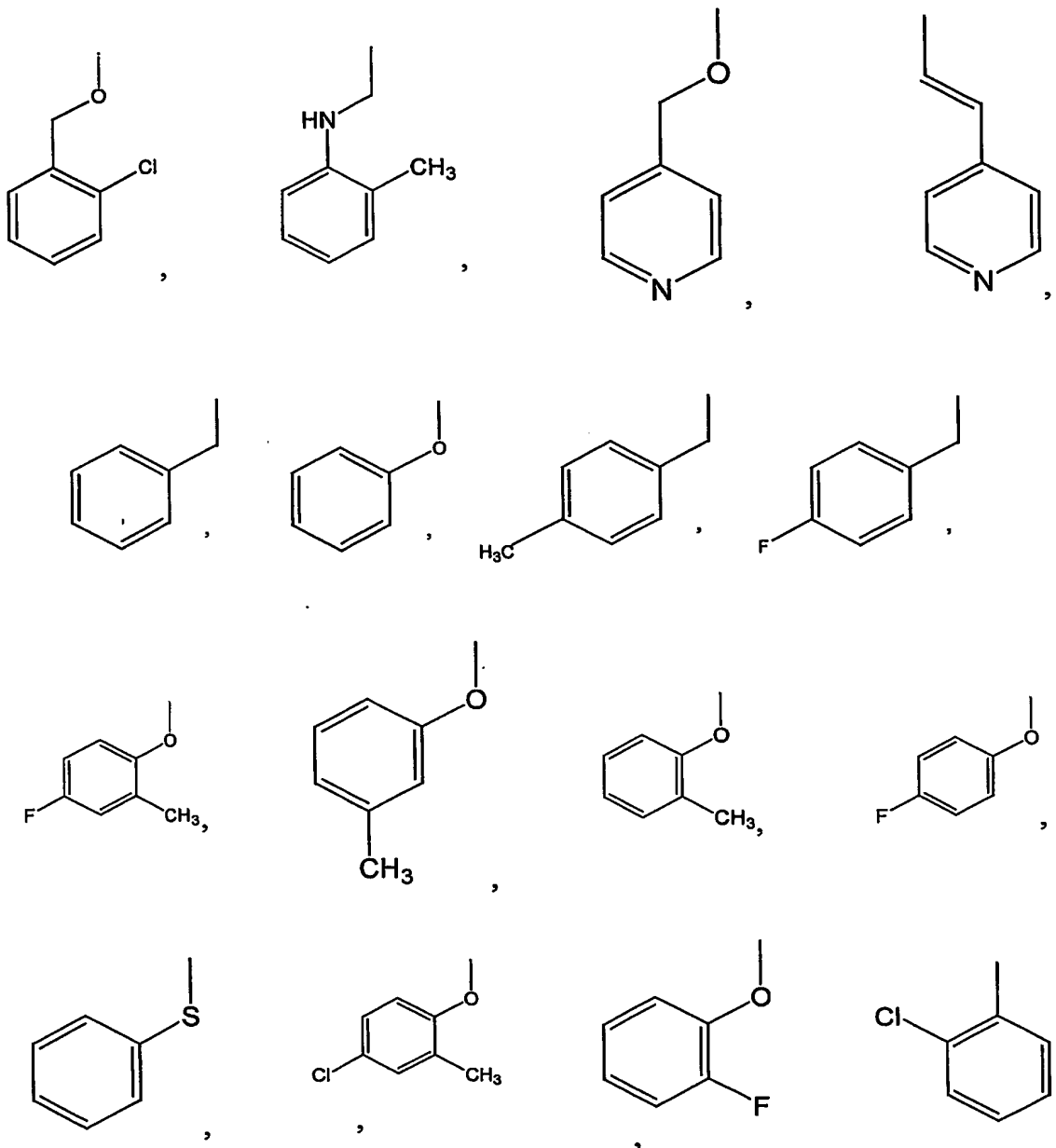


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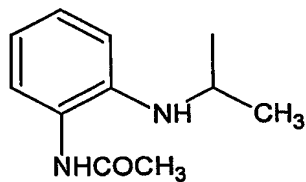
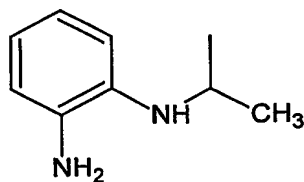
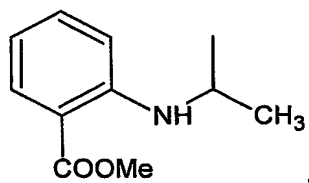
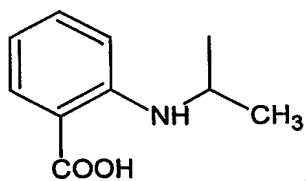
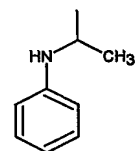
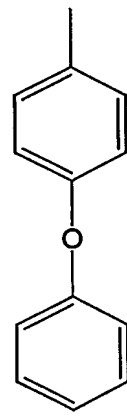
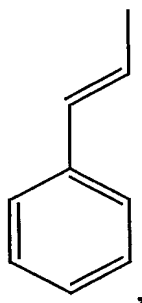
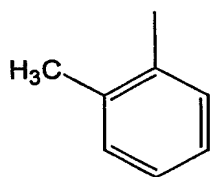
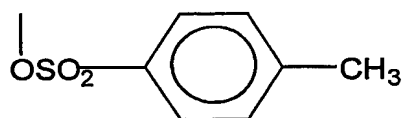
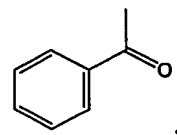
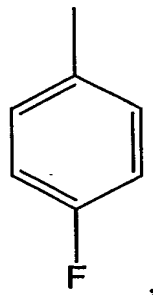
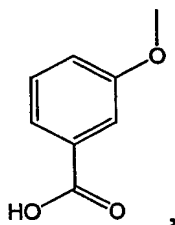
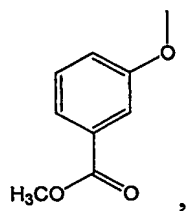


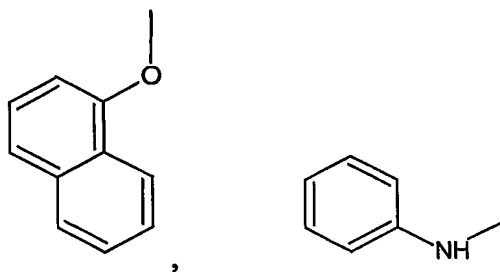
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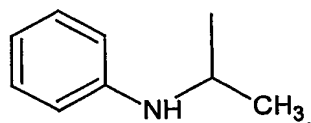


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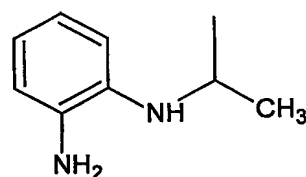




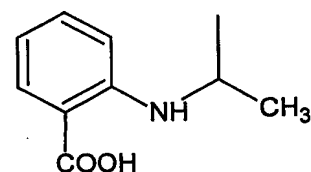
9. The compound of claim 5, wherein R is methyl and R¹ is



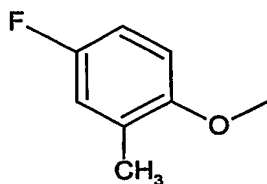
10. The compound of claim 5, wherein R is methyl and R¹ is



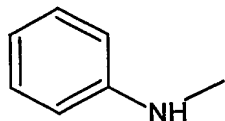
11. The compound of claim 5, wherein R is methyl and R¹ is



12. The compound of claim 5, wherein R is H and R¹ is



13. The compound of claim 5, wherein R is H and R¹ is



14. A method for inhibiting phosphoinositide 3-kinase in a patient, comprising administering to a patient an amount of the compound of claim 5 effective in inhibiting the phosphoinositide 3-kinase in the patient.

15. A method for preventing or treating cardiovascular disease comprising administering an effective amount of the compound of claim 5 to a patient in need thereof.

16. A method for preventing or treating respiratory disease comprising administering an effective amount of the compound of claim 5 to a patient in need thereof.

17. A method for preventing or treating cancer comprising administering an effective amount of the compound of claim 5 to a patient in need thereof.

18. A method for preventing or treating disease linked to disordered white blood cell function comprising administering an effective amount of the compound of claim 5 to a patient in need thereof.

19. (Deleted).

19. (Renumbered) The method of claim 4, wherein the inhibitor administered is 6-methyl-8-[1-(phenylamino)ethyl]-2-(4-pyridinyl)-4*H*-benzopyran-4-one.

20. (Renumbered) The method of claim 4, wherein the inhibitor administered is 6-methyl-8-{1-[(2-aminophenyl)amino]ethyl}-2-(4-pyridinyl)-4*H*-benzopyran-4-one.

21. (Renumbered) A compound which is (\pm)-7-methyl-2-morpholin-4-yl-9-(1-phenylaminoethyl)-pyrido[1,2-*a*]pyrimidin-4-one.

22. (Renumbered) A compound which is (\pm)-2-({1-[7-methyl-2-(morpholin-4-yl)-4-oxo-pyrido[1,2-*a*]pyrimidin-9-yl]ethyl} amino)benzoic acid.

23. (Renumbered) A compound which is (\pm)-2-({1-[7-methyl-2-(morpholin-4-yl)-4-oxo-pyrido[1,2-a]pyrimidin-9-yl]ethyl}amino)benzonitrile.
24. (Renumbered) A compound which is (\pm) methyl 2-({1-[7-methyl-2-(morpholin-4-yl)-4-oxo-pyrido[1,2-a]pyrimidin-9-yl]ethyl}amino)benzoate.
25. (Renumbered) A compound which is (\pm)-7-methyl-2-(morpholin-4-yl)-9-(1-{[2-(2*H*-tetrazol-5-yl)phenyl]amino}ethyl)-pyrido[1,2-a]pyrimid-4-one.

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